Advanced Synthesis & Catalysis

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201700073

Link to VoR: http://dx.doi.org/10.1002/adsc.201700073

10.1002/adsc.201700073

COMMUNICATION

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Concise Synthesis of Spiro[indoline-3,2'-pyrrolidine] and 1-Aza-carbazole Derivatives via Copper-Catalyzed Cyclization of Indoles

Peng-Fei Wang,‡ Chao Chen,‡ Hui Chen, Li-Shuai Han, Liu Liu, Hongbin Sun, Xiaoan Wen* and Qing-Long Xu*

Jiangsu Key Laboratory of Drug Discovery for Metabolic Disease and State Key Laboratory of Natural Medicines, China Pharmaceutical University, 24 Tongjia Xiang, Nanjing 210009, China
Fax: (+86)-25-8327-1050; E-mail: wxagj@cpu.edu.cn.com; qlxu@cpu.edu.cn
‡ These authors contributed equally.

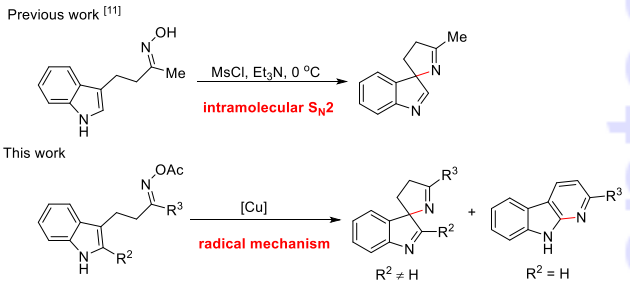
Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. A high-yielding copper-catalyzed dearomatization reaction of indole from 2-methyl indole-derived oxime acetates was realized, providing access to structurally novel spiro[indoline-3,2'-pyrrolidine] derivatives in 67-98% yields. When the C2-position of the indole was not substituted, aza-carbazole derivatives were obtained in moderate yields. This transformation provided an efficient approach to access nitrogen-containing spiroindolenine and aza-carbazole derivatives with wide substrate scope.

Keywords: Copper-catalyzed; C-N bond formation; spiroindoline; dearomatization;

The spiroindolenine and polycyclic indole moieties are embedded in several classes of natural products and biologically active compounds.[1] For the past few years, great advances have been achieved in the construction of these skeletons bearing a quaternary stereocenter at C3 position of the indole core. For the construction of these important and valuable scaffolds, transition-metal catalyzed dearomatization reactions of indole derivatives have attracted considerable attention for organic chemists.[2] Among the reported methodologies, the intramolecular allylic alkylation of indole have been developed for preparation of spiroindolenines using palladium,[3] iridium,[4] gold[5] and ruthenium[6] as the catalysts. The cascade transformation of indole-containing π-allyl species has also been utilized to build spiroindolenine derivatives in a direct manner.[3] The groups of You, Xu and Liang recently reported a palladium catalyzed dearomatizative arylation approach to spiroindolenines that involves an intramolecular nucleophilic attack by the C3 position of indole of the aryl palladium complex.[7] In a related process, spiroindolenine derivatives were obtained through electrophilic alkyne activation with a simple Lewis or π-acidic catalyst.[8] Recently, Vincent and coworkers reported a straightforward access to spiroindoline derivatives via the intramolecular hydroarylation of N-Ac indoles mediated by $FeCl_3$, which involves an umpolung of the indole C2=C3 bond.[9] We recently developed an intramolecular palladium-catalyzed dearomative arylation reaction of indole via C-H bond functionalization, providing access to structurally novel spiroindolenines.[10] Owing to the importance of spiroindolenine derivatives, the development of new methods that afford novel spiro structures with high efficiency is much desired.



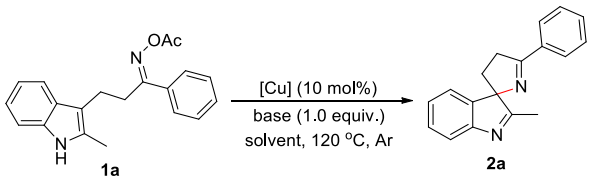
Scheme 1. Synthesis of spiro[indoline-3,2'-pyrrolidine] derivatives.

Through the strategy of indole dearomatization process, synthesis of the diazaspiroindolenine has been reported rarely. In fact, preparation of spiro[indoline-3,2'-pyrrolidine] derivatives by a intramolecular S_N2-type cyclization from β-3-indolyl ketone oximes is the only reported example (Scheme 1).[11] On the other hand, copper-catalyzed N-O bond cleavage of oxime ester has attracted considerable interest, for construction of azaheterocycles.[12] As part of our interest aimed at developing novel synthetic methodologies for the rapid construction of spirocyclic molecules,[10, 13] in this report we show that spiro[indoline-3,2'-pyrrolidine] derivatives can be efficiently obtained from β-3-indolyl ketone oxime acetates via copper catalysis. The mechanism of this

reaction is different from that of the reported ones, most of which exploit the nucleophilicity of indole C3 position. Moreover, we found that under the optimized reaction conditions indoles which lack substitution at their C2 position furnished aza-carbazole derivatives as major products.[14]

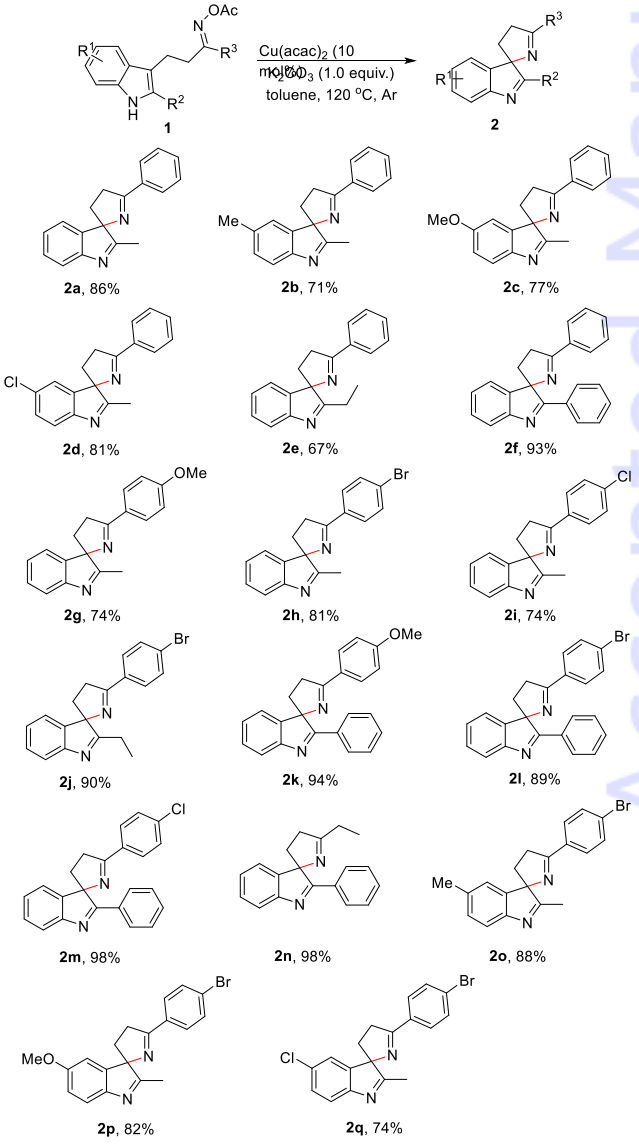
In our initial study, 2-methyl indole-derived oxime acetate **1a** was chosen as the model substrate to investigate the copper-catalyzed intramolecular cyclization reaction in toluene at 120 °C, using Cs_2CO_3 as the base. To our delight, the desired spiro[indoline-3,2'-pyrrolidine] derivative **2a** was obtained in 51% yield in the presence of CuBr under argon condition (entry 1, Table 1). Encouraged by this result, different copper complexes, including CuI, CuCl, Cu_2O, $Cu(Ac)_2$, CuO, $Cu(CH_3CN)_4PF_6$, $CuSO_4$, $Cu(OTf)_2$, $Cu(acac)_2$, were evaluated to determine their impact on reaction efficiency (entries 2-10, Table 1). We found that $Cu(acac)_2$ was the most efficient catalyst for this transformation, giving the desired product **2a** in 82% yield. A control experiment established that no reaction occurs in the absence of a copper catalyst (entry 11, Table 1). Next, the examination of different bases such as K_2CO_3, Li_2CO_3, Et_3N revealed that the base played a critical role in this reaction (entries 12-14, Table 1). K_2CO_3 was proved to be the best while the product yield was decreased to 66% without base (entry 15, Table 1). Different solvents such as DMSO, DMF, MeCN, Dioxane were also investigated, and toluene was found to be the optimal solvent (entries 16-19, Table 1). When the loading of the base or the copper catalyst was decreased to 0.5 equiv. and 5 mol%, respectively, the product was obtained in somewhat lower yields (entries 20, 22, Table 1). When the reaction was performed under air, the isolated yield was 51% that indicated potential interference (entry 21, Table 1). Finally, the optimal reaction conditions were determined as follows: substrate (1.0 equiv.), K_2CO_3 (1.0 equiv.), $Cu(acac)_2$ (10 mol%) in toluene at 120 °C under argon condition.

Table 1. Evaluation of the Reaction Conditions. [a]



entry	[Cu]	base	solvent	time (h)	yield (%) [b]
1	CuBr	Cs_2CO_3	PhMe	7	51
2	CuI	Cs_2CO_3	PhMe	7	58
3	CuCl	Cs_2CO_3	PhMe	7	62
4	Cu_2O	Cs_2CO_3	PhMe	7	39
5	$Cu(OAc)_2$	Cs_2CO_3	PhMe	7	50
6	CuO	Cs_2CO_3	PhMe	7	79
7	$Cu(CH_3CN)_4PF_6$	Cs_2CO_3	PhMe	7	61
8	$CuSO_4$	Cs_2CO_3	PhMe	7	42
9	$Cu(OTf)_2$	Cs_2CO_3	PhMe	7	67
10	$Cu(acac)_2$	Cs_2CO_3	PhMe	7	82
11 [c]	-	Cs_2CO_3	PhMe	7	NR
12	$Cu(acac)_2$	K_2CO_3	PhMe	4	86
13	$Cu(acac)_2$	Li_2CO_3	PhMe	4	80
14	$Cu(acac)_2$	Et_3N	PhMe	4	66
15 [d]	$Cu(acac)_2$	-	PhMe	4	66
16	$Cu(acac)_2$	K_2CO_3	DMSO	2	41
17	$Cu(acac)_2$	K_2CO_3	DMF	6	74
18	$Cu(acac)_2$	K_2CO_3	MeCN	12	39
19	$Cu(acac)_2$	K_2CO_3	Dioxane	12	76
20 [e]	$Cu(acac)_2$	K_2CO_3	PhMe	4	66
21 [f]	$Cu(acac)_2$	K_2CO_3	PhMe	12	51
22 [g]	$Cu(acac)_2$	K_2CO_3	PhMe	7	57

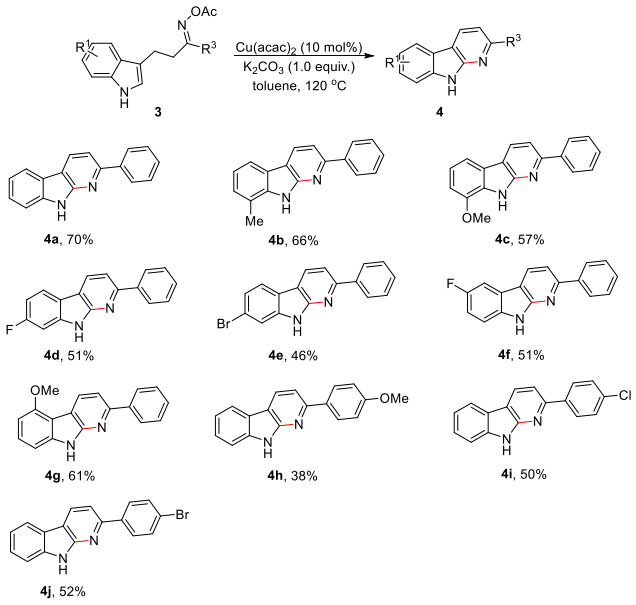
[a] Reaction conditions: **1a** (0.3 mmol), [Cu] (10 mol%), base (1.0 equiv.), solvent, 120 °C, Ar. NR = no reaction.
[b] Isolated yield.
[c] No [Cu] catalyst was added.
[d] No base was added.
[e] Using 0.5 equiv. K_2CO_3.
[f] Under Air condition.
[g] Using 5 mol% $Cu(acac)_2$.



[a] Reaction conditions: **1** (0.3 mmol), $Cu(acac)_2$ (10 mol%), K_2CO_3 (1.0 equiv.), toluene, 120 °C, Ar.

Scheme 2. Substrate scope for synthesis of spirocycles. [a]

With the optimal reaction conditions in hand, we then investigated the scope of the ketoxime acetates and the results were shown in Scheme 2. Different substituents on the benzene ring of the indole core such as methyl, methoxyl, chloro were all well-tolerated and the corresponding products were obtained in good isolated yields (**2a-2d**). The substrate **1e** bearing a ethyl group at the C2-position of the indole moiety also worked well to afford the product **2e** in 67% yield. Interestingly, when a phenyl moiety was introduced at the C2 position of the indole, product **2f** was obtained in excellent yield (93%). Next, the substitution pattern on the aromatic ring adjacent to the oxime moiety was varied (e.g., 4-OMe, 4-Br, 4-Cl) and we found that regardless of the electronic properties of this ring, all of the substrates could be smoothly converted to the corresponding products in reasonable yields (74-81%). Likewise, varying the substituents on the indole core did not have a dramatic impact on the course of the spirocyclization process and the corresponding products (**2j**-**2q**) were obtained in good to excellent yields (74-98%). In addition to structurally diverse aryl groups, alkyl groups are also well-tolerated adjacent to the oxime acetate moiety as substrate **1n**, bearing an ethyl group, furnished the desired product **2n** in 98% yield under the standard reaction conditions. Through exploring the substrate scope, we found that the substrates with phenyl group at the C2-position of the indole moiety afforded the desired products in higher yields, probably due to the favorable stability of the corresponding radical intermediates.

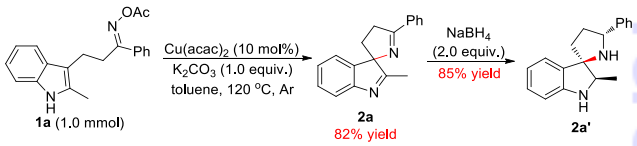


[a] Reaction conditions: **3** (0.3 mmol), $Cu(acac)_2$ (10 mol%), K_2CO_3 (1.0 equiv.), toluene, 120 °C.

Scheme 3. Substrate scope for synthesis of aza-carbazole derivatives. [a]

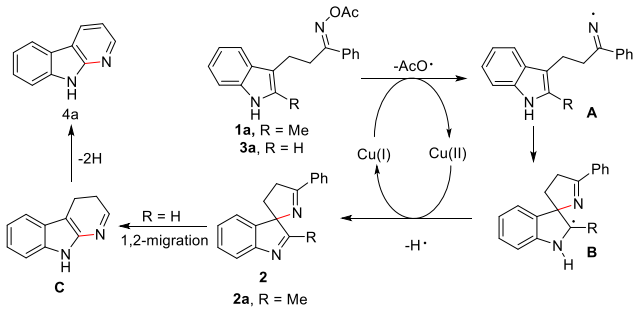
Meanwhile, the substrate bearing hydrogen at C2 position of the indole ring could provide aza-carbazole derivative **4** as the major product, therefore, further exploration of the substrate scope was performed as shown in Scheme 3. We found that reaction of C2-unsubstituted indole derivatives (**3)** could smoothly provide aza-carbazole derivatives **4a**-**4g** in good yields (51-70%) under the optimized reaction conditions. Next, substrates bearing a *para* substituent (4-OMe, 4-Cl, 4-Br) on the phenyl ring adjacent to the oxime acetate moiety were investigated. The corresponding fused pyridine products (**4h-4j**) were obtained in moderate yields (38-52%). Together, this protocol provides a new approach to aza-carbazole derivatives.

To further demonstrate the utility of this efficient spirocyclization, the reaction of **1a** was performed on a 1.0 mmol scale and product **2a** was isolated in 82% yield. Compound **2a** could be easily reduced with $NaBH_4$ to provide spiroindoline **2a'** in 85% yield (Scheme 4), and the relative configuration was confirmed by the NOE spectra (see the supporting information for details).



Scheme 4. Practical preparation and transformation of **2a**.

Based on the results outlined above and also on work already reported, we propose a radical mechanism for this transformation (Scheme 5). In the first step an imino radical is generated when Cu(I) initiates a reductive N-O bond cleavage of the ketoxime acetate **A**. Next, an intramolecular 5-exo-trig radical cyclization of intermediate **A** gives rise to intermediate **B**. Finally, single-electron oxidation of intermediate **B** by Cu(II) species forms the corresponding product spiro[indoline-3,2'-pyrrolidine] derivative and the Cu(I) catalyst is regenerated. To understand the mechanism of the reaction, we added radical scavengers to the reaction, and found that when TEMPO (20 mol%) was added, the reaction could still proceed but the product was obtained in a much lower yield (20%).[15] However, When substrate **3a** (R = H) was employed in this transformation, the unstable spiroindole was obtained, then 1,2-migration would be taken place, and many related processes *via* 1,2-migration have been reported in the literatures, [8b, 16] affording intermediate **C**, a double bond is formed by oxidizing the intermedate **C** to produce the product **4a**.



Scheme 5. Proposed mechanism.

In summary, we have developed a novel and highly efficient copper-catalyzed intramolecular dearomatization reaction of C3-substituted indoles, which allows the construction of both spiro[indoline-3,2'-pyrrolidine] and aza-carbazole derivatives by varying the substituents at the C2 position of the indole nucleus. Further work to expand the scope of this novel spirocyclization strategy and to better understand the reaction mechanism are currently ongoing in our laboratory and results will be reported in due course.

Experimental Section

To a solution of **1** or **3** (0.3 mmol) in dry toluene (3.0 mL) was add K_2CO_3 (0.3 mmol) and $Cu(acac)_2$ (0.03 mmol) into Schlenk flask under argon, and then the reaction mixture was stirred at 120 °C until complete consumption as monitored by TLC. The solvents were removed under reduced pressure, and flash chromatography was used to give the desired product.

Acknowledgements

Financial support from National Natural Science Foundation of China (grants 81373303, 81473080, 81573299 and 21502230) is gratefully acknowledged. This project was also supported by the Jiangsu Province Natural Science Foundation (BK20150688), the "111 Project" from the Ministry of Education of China, the State Administration of Foreign Expert Affairs of China (No. 111-2-07) and program for Changjiang Scholars and Innovative Research Team in University (IRT1193), Project Program of State Key Laboratory of Natural Medicines, China Pharmaceutical University (No. SKLNMZZYQ201607).

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10.1002/adsc.201700073

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Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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